REMARKS

Applicants acknowledge the Examiner's indication that elected Group II contains claims 8-12, 40-43, and 49-62.

At page 2 of the instant Office Action, the Examiner has stated that claims 8-12 and 40-43 are under consideration and that claims 49-62 "are withdrawn as being drawn to non-elected species (the entire elected set of nucleotide positions is not found in these claims)." Applicants respectfully submit that claims 49-62 are directed to the elected invention, and respectfully request clarification by the Examiner in this regard.

In the instant Office Action, claims 1-7, 13-39, 44-48, and 63-134 have been canceled, without prejudice, as being directed to a non-elected invention. Claims 40 and 49 have also been canceled herein, without prejudice. Claims 8, 41, 42, 51, 56, and 58 have been amended and new claims 135-143 have been added. Accordingly, claims 8-12, 41-43, 50-62 and 135-143 are presently pending in the application.

Support for the above amendments and new claims can be found in the specification and claims as originally filed and/or previously pending. In particular, support for new claims 136-143 may be found in the specification at, for example, page 7, line 27 through page 8, line 7 of Applicants' specification.

Cancellation of and/or amendment to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in another patent application.

Restriction Requirement

The Examiner has stated that Applicants' traversal of the Restriction Requirement dated June 19, 2003 and November 25, 2003, which required the election of a single nucleotide sequence, is found unpersuasive for the following reasons: "[t]he request for multiple sequences searched is found unpersuasive. Due to the number of these sequence requests made by Applicants in the field of biotechnology, it is practically impossible to

accommodate all of these requests. The overwhelming number of sequences poses undue search burden when more than one nucleic acid sequence is elected."

Applicants reiterate the traversal of the requirement that a single sequence be elected. However, in an effort to expedite prosecution of the application, Applicants have amended the claims to refer to SEQ ID NO:1.

Claim Objections

The Examiner has objected to claims 8-12 and 40-43 "due to the inclusion of subject matter which has been non-elected due to a restriction requirement and therefore withdrawn from consideration . . . These claims contain additional sequences with cited nucleotide positions that are not elected subject matter, such as SEQ ID NO: 3 and THBS4."

Applicants respectfully submit that the claims have been amended to remove reference to SEQ ID NO:3 or THBS4. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection.

The Examiner has also objected to claim 8 "because. . . [c]laim 8, last 2 lines, recites the phrase "or the complement thereof, or the complement thereof" which seems to be redundant."

Applicants respectfully submit that claim 8 has been amended to remove the redundant phrase. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection.

Rejection of Claims 8-12 and 40-43 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 8-12 and 40-43 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention." In particular, the Examiner is of the opinion that

> [t]he methods in the instant invention are directed to a determination of the identity of all six nucleotides in these SNP

> locations; however, it does not appear that one of skill in the art would know, for example in claim 8, which variant alleles need to be present or which combinations of these variant alleles are necessary in order for the identification of a subject who is a candidate for further diagnostic evaluation for a vascular disease or disorder. For example, if the variant allele for G334u4 (positive indicator of vascular disease) is present as well as the variant alleles of G334al6 and G334k2 (negative indicators of vascular disease which are SNPs with negative linkage disequilibrium with G334u4), does this provide a stronger case for having coronary artery disease or not?

Applicants respectfully traverse the foregoing rejection and submit that one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation for the following reasons.

Applicants respectfully submit that one of skill in the art would know which variant alleles need to be present or which combinations of these variant alleles are necessary in order for the identification of a subject who is or is not a candidate for further diagnostic evaluation for a vascular disease or disorder. Applicants' specification clearly sets forth which nucleotides are associated with an increased or decreased risk for vascular disease or indicate a subject as a candidate for further diagnostic evaluation. For example, Applicants' specification states that,

> three SNPs in the THBS1 gene (identified herein as G334u3, G334a18, and G334u5, see Table 1), are in strong linkage disequilibrium (LD) with G334u4, and are associated with increased risk of vascular disease such as CAD and MI. Two SNPs in the THBS1 gene, identified herein as G334a16, and G334k2, are in negative LD with G334u4 and have a protective effect for vascular disease, *e.g.,* a subject with the variant alleles are less likely to have vascular disease, *e.g.,* CAD or MI. (Page 12, line 12-19).

Applicants submit that one of ordinary skill in the art would be able to practice the claimed methods using only routine experimentation. However, in an effort to expedite prosecution of the application, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 8 such that it is directed to a method for identifying a subject who is a candidate for further diagnostic evaluation for a vascular disease or

disorder comprising determining the identity of one or more of the nucleotides present at nucleotide positions 55322, 53502, 60793, and/or 58445, or the full complement thereof, wherein the presence of at least one variant allele, or the full complement thereof, identifies the subject as a subject who is a candidate for further diagnostic evaluation for a vascular disease or disorder.

New claim 135 has been added which is directed to a method for identifying a subject who is ***not*** a candidate for further diagnostic evaluation for a vascular disease or disorder comprising determining the identity of one or more of the nucleotides present at nucleotide positions 52861 or 49556 of SEQ ID NO:1, or the full complement thereof, wherein the presence of at least one variant allele, or the full complement thereof, identifies the subject as a subject who is not a candidate for further diagnostic evaluation for a vascular disease or disorder.

Furthermore, in an effort to expedite prosecution, but in no way acquiescing to the Examiner's rejection, claim 40 has been canceled. Claim 41 has been amended such that it is directed to a method for diagnosing or aiding in the diagnosis of a vascular disease or disorder in a subject comprising determining the thrombospondin 1 (THBS1) genetic profile of the subject, wherein determining the subject's thrombospondin 1 (THBS1) genetic profile comprises determining the identity of one or more of the nucleotides present at nucleotide positions selected from the group consisting of: 55322, 53502, 60793, and 58445 of SEQ ID NO:1, or the full complement thereof; wherein the presence of at least one variant allele, or the full complement thereof, is indicative of an ***increased*** likelihood of a vascular disease or disorder in the subject as compared with a subject having the reference allele at one or more of these loci. Claim 51 is directed to a method of diagnosing or aiding in the diagnosis of a vascular disease or disorder in a subject comprising determining the thrombospondin 1 (THBS1) genetic profile of the subject, wherein determining the subject's thrombospondin 1 (THBS1) genetic profile comprises determining the identity of one or more of the nucleotides present at nucleotide positions 52861 or 49556 of SEQ ID NO:1, or the full complement thereof; wherein the presence of at least one variant allele, or the full complement thereof, is indicative of a ***decreased***

likelihood of a vascular disease or disorder in the subject as compared with a subject having the reference allele at one or more of these loci.

Therefore, based on the arguments and amendments set forth above, Applicants respectfully submit that one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 8-12 and 40-43 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 8-12 and 40-43 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> SEQ ID NO: 1 and its full complement meet the written description provisions of 35 U.S.C. 112, first paragraph. However, claims 8-12 and 40-43 are directed to encompass the various other types of complements of SEQ ID NO: 1 that do not meet the written description provision of 35 U.S.C. 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by these claims. . . [t]herefore, only SEQ ID NO: 1 and its full length complement, but not the full breadth of the claims 8-12 and 40-43 meet the written description provision of 35 USC 112, first paragraph.

Applicants respectfully traverse the foregoing rejection and submit that the instant specification provides sufficient written description regarding the complement of the claimed nucleotides. The instant specification sets forth the definition of a complement of a nucleotide sequence as follows:

> in one embodiment of the invention, a complement of the nucleotide sequence is provided wherein the polymorphism has been identified. For example, where there has been a single nucleotide change from an adenine to a guanine in a single strand, the complement of that strand will contain a change from a thymidine to a cytidine at the corresponding nucleotide residue (page 6, lines 17-21).

Based on the specification, Applicants respectfully submit that one skilled in the art would recognize that the inventor, at the time the application was filed, had possession of the claimed invention. However, in an effort to expedite prosecution of the application, and in no way acquiescing to the Examiner's rejection, Applicants have amended claims 8, 41, 49, 51, 56, and 58 to recite the phrase "full complement." Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 8-12 and 40-43 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." In particular, the Examiner is of the opinion that "[c]laim 40 is vague and indefinite due to the unclarity of citing an abbreviation, such as THBS1."

Applicants respectfully traverse the foregoing rejection and submit that the term THBS1 is clear and definite. In the instant specification, the term THBS1 is indicated as representing thrombospondin 1 (see Applicants' specification at page 2, lines 26-27). Furthermore, the term THBS1 is well known in the art to refer to thrombospondin 1. Therefore, the term THBS1 would be readily understood by one of ordinary skill in the art. However, in an effort to expedite prosecution of the application, and without acquiescing to the Examiner's rejection, Applicants have amended claims 40 and 41 to include the full name of thrombospondin 1. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

The Examiner has also rejected claims 8 and 41 under 35 U.S.C. §112, second paragraph, because, in the Examiner's opinion, the recitation of the phrase "the complement thereof" is vague and indefinite.

Applicants respectfully traverse the foregoing rejection and submit that the phrase "complement thereof" is clear and definite with respect to the nucleotide positions set forth in the claims. As set forth above, the instant specification describes the term complement as follows:

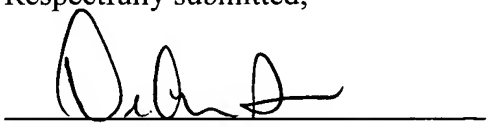
> in one embodiment of the invention, a complement of the nucleotide sequence is provided wherein the polymorphism has been identified. For example, where there has been a single nucleotide change from an adenine to a guanine in a single strand, the complement of that strand will contain a change from a thymidine to a cytidine at the corresponding nucleotide residue (page 6, lines 17-21).

Furthermore, the term complement is well known in the art. Therefore, the phrase "complement thereof," as set forth in the instant claims, would be readily understood by one of ordinary skill in the art. However, in an effort to expedite prosecution of the application, and without acquiescing to the Examiner's rejection, Applicants have amended claims 8 and 41 to recite the phrase "full complement." Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

CONCLUSION

It is respectfully submitted that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



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